UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,514	03/12/2004	Francois Spertini	30985/41486	8487

7590 12/17/2008

Jeffrey S. Sharp
MARSHALL, GERSTEIN & BORUN LLP
Sears Tower
233 S. Wacker Drive, Suite 6300
Chicago, IL 60606-6357

EXAMINER	
ROONEY, NORA MAUREEN	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,514	SPERTINI ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-63 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-63 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed on 09/26/2008 is acknowledged.

2. Claims 55-63 and 65 are pending and currently under examination as they read on a method for generating a composition of contiguous overlapping peptide fragments.

3. The following rejections are necessitated by the amendment filed on 09/26/2008.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 55-61 stand rejected and claim 63 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/88085 (PTO-892, Reference N) for the same reasons as set forth in the Office Action mailed on 06/12/2008.

WO 01/88085 teaches a method for generating a composition of contiguous overlapping peptide fragments (COPs) for a selected polypeptide allergen the improvement comprising carrying out the steps of: (1) determining candidate contiguous overlapping peptides by a method comprising: (a) conducting a computerized structural analysis of the selected polypeptide allergen to identify alpha helix, beta sheet and cysteine bridge three-dimensional structural formations (In particular, page 8, lines 5-15); (b) selecting one or more separation sites within

the sequence of the polypeptide allergen to provide candidate contiguous overlapping peptide fragments from 30 to 90 peptides in length which peptides overlap each separation site (In particular, page 2, lines 16-23) wherein said COPs present all potential T-cell epitopes but interrupt alpha helix and beta-sheet structural motifs involved in IgE binding (In particular, page 19, lines 13-29); and (2) producing said candidate contiguous overlapping peptide fragments; and (3) screening said candidate COPs by the steps of: (a) selecting COPs characterized by having a T cell stimulating activity for T cells specific for the selected polypeptide allergen which is greater than a selected minimum by contacting said COPs with T cells specific for the selected polypeptide allergen and detecting said T cell stimulating activity (In particular, page 9, line 31 to page 10, line 9); and (b) selecting COPs characterized by having an IgE binding activity for IgEs reactive with the selected polypeptide allergen which is less than a selected maximum by contacting said COPs with IgEs reactive with said selected polypeptide allergen and detecting said IgE binding activity by in vitro and in vivo tests (In particular, page 6, line 5 to page 7, line 12) of claim 55; wherein the COPs have relatively reduced levels of IgE binding activity but conserved T cell stimulating activities relative to the IgE binding and T cell stimulating activities of the allergen (In particular, page 19, lines 13-29);) of claim 56; wherein the peptides overlap each separation site by 10 amino acid residues (In particular, page 2, lines 16-23) of claim 57; wherein said COPs have a T cell stimulating index which is greater than 2 (In particular, page 9, line 31 to page 10, line 9) of claim 58; wherein said COPs are useful in inducing tolerance to said polypeptide allergen (In particular, page 6, lines 27-30) of claim 59; wherein the COPs are useful in desensitization immunotherapy (In particular, page 18, lines 9-30) of claim 60; and wherein which the IgE binding activity in vitro is measured by

immunoblotting (In particular page 24, lines 15-29) of claim 61; and wherein the IgE binding activity is measured in vivo by an intradermal test (In particular, page 6, lines 27-30, page 3, lines 8-13) of claim 63.

The reference teachings anticipate the claimed invention.

Applicant's argument filed on 09/26/2008 has been fully considered, but is not found persuasive.

Applicant argues:

> "The anticipation rejection of claims 55-61 over Spertini WO 01/88085 should be withdrawn because it neither discloses nor teaches selecting peptides with reduced IgE binding activity by use of the combination of an *in vitro* test with an *in vivo* test as required by the foregoing amendment. Although separate elements within the claimed method can be found within Spertini WO 01/88085 there is no teaching of how to select for proper peptides to be used to treat allergic subjects. Moreover, one following the teachings of Spertini WO 01/88085 would not have selected proper peptides because its use of *in vitro* IgE binding tests such as ELISA, immnoblots and dot blots, produces false negative results that use of a skin test would have avoided.
>
> Independent claim 55 has been amended to recite that the detection of IgE binding activity is by *in vitro* testing and by an *in vivo* test and as such the claim is novel over Spertini WO 01/88085 which does not disclose *in vitro* or skin testing. Instead, Spertini WO 01/88085 at page 6, lines 27-30 discloses the use of peptides to tolerize patients by subcutaneous injection and not to check for lower IgE levels. The reference at page 19, lines **13-29** of Spertini WO 01/88085 is to the ability of the peptides to stimulate IgE formation during treatment and not to check for lower IgE binding of the peptides *in vitro*.
>
> Even if Spertini WO 01/88085 were to teach *in vitro* testing for IgE binding to peptide candidates, such a disclosure would be misleading because *in vitro* testing is prone to false negatives. Thus, when Fellrath et al., J. Clin Immunol. Vol 111, No. 4, pp. 854-861 (2003) (a copy of which is attached as Exhibit A) practiced the methods of Spertini WO 01/88085 in the production ofPLA 2 bee venom peptides the results of a dot blot testing were positive for IgE binding activity. See p 858, last paragraph to p 859 first paragraph and Fig. 5 of Fellrath which depicts residual IgE binding activity for peptides LSP 1-60 and LSP 90-134 which peptides would have been discarded by practice of the claimed method. Thus, Spertini WO 01/88085 not only fails to disclose the present invention but it teaches away from it.

It is the Examiner's position that WO 01/88085 teaches selecting peptides with reduced IgE binding activity by *in vitro* and *in vivo* testing, contrary to Applicant's assertion. WO

01/88085 discloses in vitro and intradermal skin testing on page 3, lines 8-12 and page 7, lines 3-12, and page 9, lines 21 to page 10, line 8 in particular. Intradermal skin testing is performed, as is well known in the art, to determine hypersensitivity in the form of IgE production at the site of injection to the allergen used. WO 01/88085 teaches how to select for proper peptides to be used to treat allergic subjects on page 7, lines 3-12.

It is the Examiner's position that WO 01/88085 does not teach away from the instant invention. False negative results, as are well known by one of ordinary skill in the art would have been addressed by using more than one screening method, especially since the reference teaches on page 7, line 10-12 that "peptides would be analyzed for the desired activity or activities by procedures known within the art." Therefore, false positives and false negatives would both have been avoided based upon the reference's teachings. In vitro testing, even if prone to false negatives (exhibiting increased IgE binding), is the first step in selecting any antigen for administration *in vivo*. So, even if it produced a false negative result, it is a necessary step to the selection of an in vivo antigen for administration. Allergens especially require *in vitro* assessment before *in vivo* testing, given the ability of allergen and allergen derivatives to cause hypersensitivity and anaphylactic shock. Therefore, Applicant's argument that peptides that are selected to be given *in vivo* would not be tested *in vitro* is unpersuasive. Furthermore, in vitro testing that resulted in a false negative result (exhibiting increased IgE binding) would only result in the selection of fewer candidate peptides. Selection of fewer than all of the possible candidate peptides that could potentially work based upon an assessment of the results from *in vivo* and *in vitro* testing is still selection of peptides and is encompassed by the instant claims. Therefore, the rejection stands.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 55 and 61- 62 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/88085 (PTO-892; Reference N) in view of Shanti et al. (PTO-892 mailed 02/12/2007, Page 2, Reference U) for the same reasons as set forth in the Office Action mailed on 06/12/2008.

WO 01/88085 has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of "wherein the immunoblot is a dot blot" of claim 62.

Shanti et al. uses a dot-blot technique to determine IgE binding to Sa-II and tropomyosin shrimp allergen peptide fragments (In particular, page 5356, paragraph spanning left and right columns and Figure 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Shanti et al. to the teachings of WO 01/88085 to determine IgE binding activity to overlapping peptide fragments using a dot blot assy.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because the dot blot as taught by Shanti et al. is a good way to test for IgE binding activity to allergen fragments (In particular, page 5356, paragraph spanning left and right columns, abstract, Figure 1). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's argument filed on 09/26/2008 has been fully considered, but is not found persuasive.

Applicant argues:

"The rejection of claims 55 and 61-62 under 35 U.S.C. 103(a) as being unpatentable over Spertini WO 01/88085 in view of Shanti et al. (The Journal of Immunology, Vol. 151, 5354-5363, No. 10, 11/15/1993) should be withdrawn because Shanti fails to make up for the deficiencies of Spertini WO 01/88085 with respect to independent claim 55 as described above. Moreover, Shanti teaches away from the present invention by teaching that one of ordinary skill would have performed dot blots for showing the

presence of IgE able to bind to COPs. Unexpectedly, COPs do not bind under comparable experimental conditions to serum IgEs of allergic patients. Thus, the method of the claimed invention provides the selection of peptides which, contrary to Shanti's peptides, do not bind IgE on dot blots!

To further elaborate, a positive result with dot blots indicates IgE binding. A negative result, however, may depend upon the technical setup and taken alone is not proof of lowered IgE binding. It could be a false negative! The claimed method which combines *in vitro* assays such as ELISA or dot blots with skin tests ensures the selection of peptides with low IgE binding activity that can be used at high dosages to safely treat patients. Accordingly, the rejection of claims 55 and 61-62 should be withdrawn."

It is the Examiner's position that Shanti et al. is only being used for its teaching that dot blotting is an *in vitro* method used to assess IgE binding to allergens and allergen fragments. Shanti et al. is not being used to teach how to select peptides based upon the presence or absence of IgE binding. Therefore, the rejection stands.

8. Claims 55, 63 and 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/88085 in view of Spertini et al. (IDS filed on 07/26/2004).

WO 01/88085 has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of "wherein the intradermal test is an immediate intradermal (ID) test wherein COPs are selected which have a wheal diameter less than or equal to 5 mm at a peptide concentration of greater than 0.1 pg/ml and no flare reaction" of claim 65.

Spertini et al. teaches the intradermal injection of three long (44-60 amino acid long) overlapping peptides at a peptide concentration of .1 μg/ml in 9 patients. Only 3 of the patients exhibited a positive reaction at day 70. The reference is silent as to what is defined as a positive

reaction, but 6 of the 9 patients exhibited no reaction. Therefore, 6 of the patients had no reaction, so they exhibited no flare reaction and a wheal diameter of less than 5mm in response to the 1 pg/ml intradermal injection.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Spertini et al. to those of WO 01/88085 in order to measure the IgE binding activity of the long overlapping peptides in vivo data at a relevant concentration because in vivo data more reliably confirms the applicability of the long overlapping peptides for an effective immunotherapy technique. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5- 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's argument filed on 09/26/2008 has been fully considered, but is not found persuasive.

Applicant argues:

"Spertini C23 fails to teach how its COPs were selected and it fails to describe what constitutes "positiveness" in intradermal tests or teach testing for a 5 mm wheal and flare reaction as recited in Applicants' claims. While intradermal tests were known as routine tests to verify skin reactivity during treatment Spertini C23 fails to teach the use of such tests as a method for selecting proper COPs. Moreover, skin tests alone will not provide the peptides of the present invention.

As was discussed above with respect to Fellrath (which is the publication which followed the abstract of Spertini C23) the peptides identified in Spertini C23 would not have been selected using the method of the claimed invention because they show reactivity on dot blots (detectable IgE binding on dot blots and accordingly 3 subjects showing reactivity after treatment with the peptides.) As a further example, peptide LSP 90-134 of Fellrath contains a disulfide bridge as seen by computer structure prediction. It binds IgE *in vitro* as seen by dot blots in Fig. 5 of Fellrath and would not be optimal for treatment and would not have been selected by practice of the claimed invention. "

It is the Examiner's position that Spertini et al. is only being used for its teaching of intradermal injection of peptides at a peptide concentration of .1 μg/ml and that some patients exhibited no reaction. Contrary to Applicant's assertion, Spertini need not teach what they assessed as positive. Both in the instant claims and the reference are concerned with peptides that produce limited or no reactions. WO 01/88085 teaches selecting the peptides based on intradermal testing and Spertini et al. teaches the technique of intradermal skin testing recited in the claims. The intradermal skin test result of no reaction at a peptide concentration of .1 μg/ml can be used to select candidate peptides in the method taught by WO 01/88085. Therefore, the rejection stands.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 12, 2008
Nora M. Rooney
Patent Examiner
Technology Center 1600

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644